UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE

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MEETING NO. 54

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Thursday, November 16, 2000

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The Advisory Committee met in Conference Room 1066, 5630 Fishers Lane, Rockville, Maryland, at 10:00 a.m., in closed session, Dr. Robert Stern, Acting Chairman, presiding.

PRESENT:

ROBERT S. STERN, M.D., Acting Chair

ELIZABETH A. ABEL, M.D., Consultant

MICHAEL BIGBY, M.D., Guest

ROSELYN EPPS, M.D., Consultant

PRESENT (Continued):

HENRY W. LIM, M.D., Member

JOEL MINDEL, M.D., Ph.D., Consultant

EVA SIMMONS-O'BRIEN, M.D., Member

MING T. TANG, Ph.D., Consultant

JAIME HENRIQUEZ, Executive Secretary

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(10:02 a.m.)

ACTING CHAIRMAN STERN: Hello. I'm Robert Stern, Acting Chair of the Dermatologic and Ophthalmologic Drugs Advisory Committee. I'd like to call Meeting No. 54 to order and welcome everyone.

This morning and this afternoon we'll be discussing NDA 50-777 from Fujisawa Healthcare, a product for the short and long-term treatment of signs and symptoms of atopic dermatitis and pediatric patients two years of age and older.

I'd like to begin with everyone around the table introducing themselves.

DR. BIGBY: I'm Michael Bigby, dermatologist from Boston.

DR. MINDEL: Joel Mindel, an ophthalmologist and pharmacologist from Mount Sinai, New York.

DR. SIMMONS-O'BRIEN: Eva Simmons-O'Brien, dermatologist at Johns Hopkins University, School of Medicine.

DR. TANG: Ming Tang, biostatistician, St.

Jude Children's Research Hospital, Memphis, Tennessee.

ACTING CHAIRMAN STERN: Robert Stern from the Beth Israel Deaconess Medical Center in Boston, a dermatologist.

MR. HENRIQUEZ: Jaime Henriquez from the FDA.

DR. LIM: Henry Lim, dermatology, Henry Ford Hospital, Detroit, Michigan.

DR. ABEL: Elizabeth Abel, clinical professor of dermatology at Stanford, California, and in private practice, Mountain View, California.

DR. EPPS: Roselyn Epps, pediatric dermatology, head of Pediatric Dermatology, Children's National Medical Center, Washington, D.C.

DR. BULL: Jonca Bull, Deputy Office Director, Office of Drug Evaluation V in the Center for Drug Evaluation and Research.

DR. WILKIN: Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products, ODE V, CDER, FDA.

DR. OKUN: Marty Okun, clinical team leader, Division of Dermatologic and Dental Drug

Products.

ACTING CHAIRMAN STERN: Thank you.

And now I'd like to ask Mr. Henriquez to tell us about the conflict of interest statements.

MR. HENRIQUEZ: The following announcement addresses the issue of conflict of interest with regards to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interest in firms related by the Center of Drug Evaluation Research present no potential for a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 USC 208(b), full waivers have been granted to Dr. Joel Mindel and Dr. Robert Stern. A copy of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office located in Room 12A-30 of the Parklawn Building.

In the event that the discussions involve

any other products or firms not already on the agenda for which the FDA participants has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvements with any firms whose products they may wish to comment upon.

Thank you.

ACTING CHAIRMAN STERN: Thank you.

And Dr. Wilkin will provide us now with an overview of the issues of this meeting.

DR. WILKIN: Often the agency is very interested in the Advisory Committee comments and advice on significant new treatments, and this is a new treatment. It's a new kind of modality. It's a topical immune suppressant for atopic dermatitis.

The active agent is tacrolimus. The sponsor is proposing two concentrations, a .03 percent and a .1 percent, and the way we think about these issues within the agency, we're actually presenting

the same paradigm to the committee. At the beginning, we consider the question is there efficacy, and so the first question: is there effectiveness of Protopic 0.3 percent, the lower concentration, in the treatment of atopic dermatitis? In other words, is it superior to its vehicle?

And then if the answer to that is yes, we continue on with other questions. And the second question is: is there sufficient evidence for superior effectiveness of Protopic, 0.1 percent, the higher concentration, compared to the 0.3 percent, in adults and in children? And we would ask for those answers separately.

The third question is: has the safety profit of Protopic in the treatment of atopic dermatitis been adequately determined for unrestricted chronic therapy as a first line treatment in adults for both concentrations, for children for both concentrations?

And I would emphasize that this particular question is not asking is it safe. It's asking has the safety profile been adequately determined because

that's the question one asks before then you go on and ask the question about safety.

And the question about safety is really imbedded into the risk-benefit calculus in the fourth question. The fourth question is: the proposed indication for Protopic, which would allow for both concentrations, for unrestricted chronic therapy, as a first line treatment of atopic dermatitis in adults and children two years and older, may be deconstructed into the following elements, which may be reconstructed into the indications.

And so what we've done for children two years and up and for adults, if you could go through and give us advice on what you think is appropriate, unrestricted chronic versus time limited acute therapy; first line versus second line treatment; the lower concentration,; the higher concentration or both or neither for a particular age subset; and then from that we can reconstruct the indication and so we can get to: is approval of Protopic recommended, and if so, under what conditions, concentrations, first versus second line, chronic versus time limited, acute

therapy, and in which age groups?

And then in the deliberation regarding all of these different elements and the indication, you may come up with items that you think some additional studies would be helpful to inform labeling. So our final question is: are there additional studies needed to provide information important for the labeling for Protopic? If so, what studies are recommended?

And we've suggested some areas to think about, but you're not limited to these. You could come up with additional ones from what you hear today and what you've read.

Consider the issues of lymphoma, local suppression of immunity, photocarcinogenesis, and so on.

Thank you.

ACTING CHAIRMAN STERN: Thank you.

I'd like to thank both the sponsor and the FDA for providing us both with comprehensive materials and also providing them in a very timely manner that permitted us to review them other than in our hotel

room the night before the meeting, and that actually has been very helpful at least to me.

And what I'd like to do next is take the liberty of the chair and expand a little bit on my perception of what the issues are, an overview of the issues based on my reading of both the sponsor's and the FDA's documents, where at least now I think the issues are so that perhaps both the sponsor and the agency can address those as we go along, and then, of course, there will be time for questions and further discussion after the presentations.

Could I have the first slide, please?

Well, as Jonathan has mentioned, I think the issue here is really: is the .1 percent superior to the .03 percent?

And in my reading of the data, the significantly better outcomes were only in subgroup analyses that were done post hoc, and in most of these subgroup analyses, the magnitude of difference in effect was small between the two, and many of these significantly better outcomes were, in fact, no longer significant after correction for multiple comparisons.

As I read -- next slide, please -- as I read the data, one subgroup seemed to stand out with significance even after appropriate correction for multiple comparisons, which was those adults with the greatest extent of disease and greatest severity, and this led me to the reflection, is: could this be a systemic effect due to the greater absorption with resulting both direct cutaneous and also systemic immune effects or much higher local levels accounting for this difference in this subgroup?

And, of course, the question here is: what are the safety implications of either greater degrees of local or systemic immunosuppression as the result of widespread use of the product in people with greatest extent and severity of disease most likely to absorb the product?

Next slide, please.

I had a few issues in terms of short-term concerns. One is bacterial infections. We know that people with atopic eczema often carry Staph. aureus, and in fact, often develop impetigo. As I read the data, it seemed that people with what were considered

to be active skin infections and recent antimicrobial therapy were excluded from the trials.

Given this, I asked myself: what in a more widespread community risk are the possible effects both with respect to increase in infection and spread of resistant strains from local Protopic use in patients who might have Staph.

Next slide, please.

My other concerns or issues were what about its effect on viral cutaneous illnesses, and there was a difference reported between the frequency of chicken pox VZV infections in the placebo and the drug treated group, and I'd like to hear a little bit more about that difference and how it was attributed to an outbreak of chicken pox and how we can be sure that's what was going on.

And I guess one thing, as much in my anecdotage (phonetic), one thing that concerned me was really rather little data with HSV or eczema herpeticum addressing in the trial. Given that I've never been an investigator and only practice one day a week and in one patient who came to see me that

person was on an open label trial at another institution in town and had classic beginnings of eczema herpeticum near the eye and knew he was on Protopic topically; so I'd like to hear a little bit more about the HSV story in terms of frequency of recurrences, spread, need for antiviral therapy, and about that.

Next slide, please.

I think the longer term issues are really long-term safety and lymphoma, as Dr. Wilkin has mentioned. Because of my interest, I think, non-melanoma skin cancer is an issue when you have immunosuppression, and I'd like to talk about that for a moment.

And as I understand it, there seems to be a tendency towards perhaps recommending minimizing exposure to sunlight while using the product, and one has to ask: is that the kind of safety we need in long-term use?

So next slide, please.

So I'd like to give my perspective on skin cancer and immunosuppression. The first is: what

kinds of tumors are we concerned about there? What length of exposure is significant? Is simultaneous exposure to UV and the immunosuppressive therapy the key issue? That is, is it order dependent? What is the timing? And might younger patients be at particularly high risk?

So in the next slide, in one slide this is my perception about systemic immunosuppression in transplant patients and skin cancer risk. Squamous cell carcinoma risk is certainly increased. The risk is greatest on sun exposed sites. It begins to increase within a few years of therapy, and in fact, even in low risk populations, such as people living in Scandinavia, at tumor transplant doses, which are mainly kidney, not heart or liver transplant doses, within two years there are about 50-fold increases in the risk of skin cancer, squamous cell carcinoma, and beginning about five years, it's about a 100-fold increase in risk. So very substantial increases.

Fortunately, I think even in people who are undergoing systemic immunosuppression, melanoma does not seem to be an issue, and if there are robust

data about the effect of long-term immunosuppression on basal cell as aside from case reports, I wish someone would tell me about them.

Next slide, please.

Well, we know that for the most part with this agent in most patients we're talking about cutaneous immunosuppression. So the question is: what is the possible relevance of our experience with systemic immunosuppression to an agent that appears to in most cases have relatively little systemic, at least non-regional systemic effects?

I think there's reasonable information that immunosuppression limited to the skin may be sufficient to increase skin cancer risk, and the reason the evidence for this are a couple of things.

If you look at PUVA, Sorlens (phonetic), and UVA, which are definitely immunosuppressive in the skin, but not systemically by a whole variety of experiments, squamous cell carcinoma began to occur too quickly to be attributable only to the mutagenic effects of the drug.

And, in fact, if you look at a nice

ordering experiment in people with CTCL, if you look at the literature and you look at individuals who are exposed to a very potent mutagen, topical nitrogen mustard, for the treatment of this tumor and they have PUVA afterwards, they often -- there's a number of reports, quite persuasive, of the very rapid emergency of many squamous cell carcinomas.

Whereas, if you do it in the other order, you give them PUVA first and then the very potent mutagen, very many fewer squamous cells emerge. So cutaneous immunosuppression probably has a substantial effect if mutagenesis has often occurred.

Next slide, please.

So I think what we think we know is that it may be that long-term use of topical immunosuppressive agents may increase squamous cell carcinoma risk,a nd based on the evidence, I think it may be that the greatest increase is in areas with the greatest prior exposure or, in fact, perhaps concomitant exposure to UV, the face, arms, hand, upper chest, upper back, and one has to remember with this product that in reading the materials, one of its

putative advantages over existing therapies, in fact, the ability to use it on especially the face where the alternative agents have undesirable long term effects.

Next slide, please.

Some things we do not know, which I think are important and perhaps the sponsor can help us with, is to what extent simultaneous UV and immunosuppressive therapy the major risk factor for increased skin cancer in immunosuppression and should our greater concern be both the survival and proliferation of greater numbers of UV mutated keratinocytes due to immunosuppression and the eventual or sooner development of tumors.

So this can be in either of two cases, one with simultaneous exposure, basically mutated cells that would have otherwise in some way been removed from the epidermis and not had a chance in years hence to go on to tumors surviving and going on at greater frequency.

And the other is for already mutated cells, will cutaneous immunosuppression have some of them go on to tumors either in greater numbers or

sooner.

And so in conclusion, to me with perhaps everyone always has their biases about what they think about a lot of the time is I think it would be important for us to address concerns about the -- on the last slide. I'm sorry. No, that's it -- we must be concerned that the long-term use of this agent might increase skin cancer, and we have to be concerned about that risk being especially great in areas of the body where there's substantial past or current exposure to UV for therapeutic agents used to treat -- that are mutagenic -- that are used to treat atopic dermatitis.

And we don't know whether we should be more or less concerned about younger patients. I think one always has to be more concerned about potential agents that impact on cancer in young people because they have a longer life expectancy for these agents, that this increased risk could manifest itself.

In addition, at least with UV there may be some differences over development in terms of the

eventual carcinogenic risk of certain exposures between young people and older people, even beyond just more years at risk in a younger person.

With that, I'd like to ask the sponsor to present, and the first presenter is Dr. Jerry Johnson.

DR. JOHNSON: Good morning. My name is Jerry Johnson, and I'm the Vice President of Regulatory Affairs, Quality and Safety at Fujisawa Healthcare, and the sponsor of the tacrolimus ointment NDA.

I would like to thank you, the Advisory Committee, for your time and the opportunity to present to you a summary of our information relating to the use of tacrolimus ointment for the primary treatment of the signs and symptoms of atopic dermatitis in adults and children.

Previously, intravenous and oral formulations of tacrolimus were developed by Fujisawa Healthcare, Incorporated, and approved and marketed as Prograf for the prevention of organ rejection in transplant recipients.

Tacrolimus ointment is a topical

formulation of tacrolimus developed specifically for the treatment of atopic dermatitis. Tacrolimus ointment is the first in a new class of nonsteroidal topical immunomodulators, and tacrolimus ointment, Protopic, received marketing approval in Japan in June of 1999.

In this worldwide development program, more than 4,000 individuals have participated in 28 clinical trials, and data from this program were presented in the tacrolimus ointment NDA and in your briefing document that you've already read.

Our presentation today will focus on the five core studies of that NDA which comprise the primary support for the safety and effectiveness of tacrolimus ointment.

In the United States, Fujisawa Healthcare submitted the IND for tacrolimus ointment in December of 1994. FHI, Fujisawa Healthcare, met with FDA at an end of Phase II meeting in October 1996, and during this meeting the pivotal clinical studies supporting the NDA were agreed upon with the definition of the primary endpoint.

A pre-NDA meeting was held in April of 1999, and FHI submitted the tacrolimus ointment, 0.3 percent and .1 percent, to the FDA on September 9th, 1999.

Atopic dermatitis is a chronic, life altering disease affecting 15 million children and adults in the United States and is characterized by painfully red, swollen, itchy, flaky skin, and in some cases the itching and redness is so vast and intense that sufferers can scratch themselves to such an extent that the risk of secondary infections increases.

The visibility of eczema can lead to a low self-esteem among these patients and the inability to interact with others, especially in children and teenagers.

Most atopic dermatitis cases are diagnosed early in childhood. Many of these patients live with their disease throughout their entire lives, and since 1970, the prevalence of atopic dermatitis has nearly tripled.

For the past 40 years, corticosteroids

have been the mainstay of therapy for atopic dermatitis. However, current treatment options are limited, especially in children, and frequently provide suboptimal control, particularly with long-term use.

Our presentation today will show that tacrolimus ointment fills a current therapeutic need for a safe and effective, topical, nonsteroidal ointment for the atopic dermatitis. Sine this product is effective monotherapy, it has an excellent safety profile for use after one year and can be safely used in children, even children as young as two years of age.

Our presentation today will include Dr. William Fitzsimmons, Vice President, Drug Development Project Management, who will present pharmacological information most relevant to tacrolimus ointment, followed by Dr. Ira Lawrence, Senior Vice President of Research and Development, who will present our clinical efficacy and safety data.

The formal presentations will be followed by a question and answer session.

We also have with us today Dr. Donald Forbes, Senior Executive Photobiologist at Argus Labs, developer of the current standard mouse model for photocarcinogenicity testing; Dr. Amy Paller, Chief, Division of Pediatric Dermatology and professor of pediatrics of Northwestern University Medical School who participated in two of the pediatric trials that will be discussed today; and Dr. Lode Swinnen, professor of medicine, Division of Hematology/Oncology of Loyola University Medical Center.

Fujisawa is very proud of this development program. We are excited that tacrolimus ointment will provide the first new treatment option in several decades for this chronic, life altering disease.

The FDA has posed several questions to you today. These are somewhat paraphrased, but is Protopic, .03 percent, effective in the treatment of atopic dermatitis?

Is the .1 percent concentration more effective than the .03 percent concentration in adults, in children?

Is Protopic safe for unrestricted chronic

therapy as a first line treatment in adults for both concentrations? In children, for both concentrations?

Is the approval of Protopic recommended, and if so, under what conditions and for which age groups?

And are there additional studies needed for the labeling of Protopic, and what are they?

We believe that our presentation will satisfactorily address all of these questions.

Dr. Fitzsimmons will begin our presentation with a summary of the pharmacology and toxicology of tacrolimus ointment. He will briefly summarize the mechanism of action of tacrolimus, followed by a presentation of the nonclinical data and their relevance to the clinical situation with regard to the hypothetical potential for events associated with the systemic administration of tacrolimus.

His presentation will then move to clinical pharmacology, focusing on a topic of particular interest with this drug, namely, blood concentrations following topical application.

Thank you.

Dr. Fitzsimmons.

DR. FITZSIMMONS: Thank you, Dr. Johnson.

Good morning. Tacrolimus ointment was developed specifically for the treatment of atopic dermatitis. Atopic dermatitis is a T cell mediated disorder involving a disregulation of IgE.

Tacrolimus acts directly on T lymphocytes, especially CD-4 positive cells, by inhibiting calcineurin. Calcineurin plays an essential role in the intracellular signal transduction pathway leading to the transcriptional activation of genes that encode for the cytokines associated with atopic dermatitis.

Additionally, tacrolimus decreases the inflammatory mediator release from skin mast cells and basophils.

As you know, nonclinical studies are an integral part of drug development. In this context, tacrolimus ointment was evaluated in an extensive and comprehensive topical pharmacology and toxicity program in several animal species.

The program was conducted over a wide dose range and included durations of application extending

from acute to lifetime exposure. Of the 27 studies conducted, there are three studies that were chronic and by that fact warrant some attention. These include a 104-week topical carcinogenicity study in B6C3F1 mice, a 52-week photocarcinogenicity study in hairless mice, and a 52-week topical toxicity study in micropigs.

In the topical carcinogenicity study, male and female B6C2F1 mice were treated for at least 104 weeks, 24 months, essentially over the lifetime of the animal. There was no increase in skin tumors observed with tacrolimus treatment. Tacrolimus ointment does not have a potential to induce skin tumors in this model.

The systemic exposure to tacrolimus blood levels in these mice was high, 89 times higher than one would typically observe in patients with moderate to severe atopic dermatitis.

This is not unexpected since it is known that rodents have a much more permeable skin than man, as well as other animal species.

One consequence of the high blood levels

in these mice was an increased incidence of non-cutaneous lymphomas at the 0.1 percent concentration. These lymphomas were not concentrated at the application site. The increased rate of lymphomas is clearly caused by the high skin permeability and subsequent high blood levels in mice over prolonged periods of time, resulting in systemic immunosuppression.

This is different than humans where the skin permeability is dramatically less, and blood levels of this magnitude and systemic immunosuppression are not seen.

A 52-week photocarcinogenicity study in hairless mice is now routinely used in the development program of all topical drug products. Please note that this model requires that all animals in all dose groups develop skin tumors. The primary metric is the median time to tumor onset relative to the control.

As you can see in this slide, the median time to tumor onset is decreased from 42 weeks in the control group to a range of 34 to 35 weeks in the vehicle .03 and .1 percent groups. For the 0.3 and

one percent groups, a further reduction in the onset time to 31 weeks is seen.

Also, the tumor amplification factor is increased to 1.3 in the vehicle .03 and .1 percent groups and 1.5 in the .3 and one percent groups.

Although providing a consistent approach to evaluate the photocarcinogenic potential, this model is still undeveloped as to the relevance of the findings to humans.

Several currently marketed topical products have produced a reduction in time to tumor onset in this model. Similar to these products, we recommend that patients applying tacrolimus ointment minimize or avoid exposure to natural or artificial sunlight and use appropriate protective measures, for example, sunscreens and protective clothing.

The 52-week topical toxicity study in micropigs specifically investigated changes, both topical and systemic, in an animal species that allowed a juvenile to adult evaluation. The skin of the micropig is considered to be the closest to that of humans in terms of permeability and topical

response.

Absorption following topical application based on AUC and blood concentrations is similar to humans, less than one percent.

In addition, the blood levels following topical application of 0.1 percent tacrolimus ointment are similar to those documented in human patients. Therefore, in contrast to the mouse studies, the micropig allows assessment of the dermal and systemic toxicity of tacrolimus ointment with absorption and blood levels similar to atopic dermatitis patients.

In this large animal model, there were no noteworthy topical or systemic findings attributable to tacrolimus.

To summarize the nonclinical findings, first, it has been established that tacrolimus is neither a mutagen nor a carcinogen. Consistent with this, the dermal oncogenicity study has shown on increase in the incidence of skin tumors.

In mice with prolonged exposure to high tacrolimus blood levels, immunosuppression results in increased risk of lymphoma.

In a mouse model of photocarcinogenicity, tacrolimus vehicle .03 and .1 percent concentrations shortened the time to tumor onset by a similar amount. Although the clinical relevance is unknown, appropriate protection from the sun is warranted.

And in an animal model which closely mimics the human situation, micropigs, there are no noteworthy topical or systemic effects attributable to tacrolimus.

I would now like to move from animals to humans and present clinical data on the pharmacology of tacrolimus ointment. In six patch test studies in health volunteers and two pharmacodynamic studies in atopic dermatitis patients, tacrolimus ointment was shown not to induce contact hypersensitivity, phototoxicity, or photosensitization.

In addition, tacrolimus ointment does not reduce collagen synthesis or skin thickness.

The results of pharmacokinetic and clinical studies in which blood concentrations were evaluated indicate that there is minimal absorption into the systemic circulation following topical

application of tacrolimus ointment.

For example, a pharmacokinetic study was conducted in 39 atopic dermatitis patients, 31 adults and eight children between the ages of five and 11 years. Patient supplied .3 percent tacrolimus ointment once daily on the days of pharmacokinetic evaluation, days one and eight, and twice daily on days two through seven.

Note that this concentration is three to ten times that of the proposed commercial concentration.

The protocol defined area of application was 50 or 100 square centimeters in children and ranged from 100 to 5,000 square centimeters in adults.

Absorption was minimal. Absolute bioavailability of less than or equal to .5 percent following topical application, and there was no evidence of systemic accumulation.

This low level of absorption was supported by data from our Phase II and III trials. In clinical trials, blood was collected during the course of the study for a determination of tacrolimus blood

concentrations at various times after application of .03 or .1 percent tacrolimus ointment.

The next three slides show the frequency of quantifiable blood concentrations in U.S. clinical studies. This frequency distribution is based on the highest individual concentration observed in any individual patient any time during the treatment.

This first slide shows the frequency distribution for the .03 percent concentration in our Phase III studies where blood was collected at weeks one, three, and 12. Note that 70 percent of the adults and 88 percent of the children applying .03 percent tacrolimus ointment did not have quantifiable levels. That is, the highest concentration observed was below .5 nanograms per mL, the limit of quantitation for the assay.

Only two adult patients, one percent, had a level of five nanograms per mL or higher, and this concentration was transient.

Expanding this analysis to highlight the 78 pediatric patients from our Phase II and III studies who received the intended concentration for

pediatrics, .03 percent tacrolimus ointment, 87 percent had concentrations less than 0.5 nanograms per mL. No pediatric patient had a concentration greater than or equal to two nanograms per mL, and there was only one patient who had a concentration higher than one, which was 1.19 nanograms per mL.

This slide shows the frequency distribution for the .1 percent concentration from our Phase III trials. Fifty-nine percent of the adults and 80 percent of the children applying .1 percent tacrolimus ointment did not have quantifiable levels. Note that only one adult patient, .5 percent, had a level of five nanograms per mL or higher, and again, this concentration was transient.

In all three U.S. Phase III trials for patients applying either .03 or .1 percent tacrolimus ointment, a total of only three adult patients, .7 percent, and no pediatric patients had a level of five nanograms per mL or higher, and this concentration was not experienced for a prolonged period but only a single sampling time and in one blood sample, a total of three samples out of 1,156 collected.

To put these concentrations into perspective, transplant patients are maintained for their lifetime on oral or intravenous doses of tacrolimus which result in minimum or trough concentrations ranging from five to 20 nanograms per mL.

If we now shift from the frequency distribution to mean concentration data, this slide shows the mean tacrolimus blood concentration at evaluation time points during the course of the 12-week double blind and up to one year open label Phase III studies. These studies form the core of our NDA submission.

There was no indication of systemic accumulation with use up to one year. Mean concentrations were lower in pediatric patients compared with adult patients, even at the 0.1 percent concentration.

Additionally, mean blood concentrations were below 0.5 nanograms per mL at all time points. These mean concentrations are less than one-tenth the lower bound of the target trough concentrations in

transplantations.

To supplement this analysis, we performed a population pharmacokinetic study which included data from our six U.S. Phase III trials during which blood was collected over a treatment period of three to 12 weeks. This analysis allows one to model the average blood concentration that would be seen in atopic dermatitis patients.

For patients in these six studies, the average percent body surface area affected was 43 percent. Based on this model, there was minimum absorption, and the population average steady state tacrolimus concentration was .25 nanograms per mL. If you take this average concentration of .25 and multiply by the 24 hours in a day, you can calculate an area under the curve of six nanogram hours per mL.

Additionally, we ran this analysis using only pediatric patients as young as two years. The average concentration in pediatrics was .21 nanograms per mL.

One can use the estimated AUC determined in this population PK model as a measure of what would

be the typical systemic exposure to tacrolimus following topical application in both adult and pediatric patients with moderate to severe AD.

Additionally, there are data available from two recently conducted European pharmacokinetic studies in adult and pediatric atopic dermatitis patients in which the effect of increasing body surface area on blood concentrations was evaluated.

The highest mean AUC over 24 hours observed in these two studies was 20 nanogram hours per mL in a group of adult patients treating the highest affected body surface area. The mean AUC in pediatrics was lower than in adults.

These data can be used to create a hypothetical worst case scenario by making three assumptions: that atopic dermatitis lesions do not heal; that the percentage of body surface area affected does not decrease with treatment; and, therefore, quantifiable blood concentrations are observed over prolonged periods of time.

All of these assumptions are contrary to clinical evidence. the typical case and hypothetical

worst case can be used to estimate relative differences in blood concentrations when evaluating the potential in atopic dermatitis patients for events that have been associated with systemic administration of tacrolimus.

In order to make this comparison, we analyzed the cumulative AUC for blood level exposure in an average transplant patient, a transplant recipient developing a lympoproliferative disorder, and the mice who develop lymphoma in the dermal oncogenicity study.

While orally of intravenously administered tacrolimus is not a mutagen nor a carcinogen, post transplant lymphoproliferative disorder or PTLD has been observed in a small percentage of transplant recipients, less than five percent. PTLD is associated with intense and excessive immunosuppression and has been reported for a variety of regimens designed to prevent graft rejection.

On average, transplant patients develop PTLD at 122 days post transplant. So we use this as the duration of treatment in these models.

The cumulative exposure in each of these groups is shown on this slide. For the average transplant recipient receiving tacrolimus, the cumulative systemic exposure to tacrolimus is 75-fold greater than the typical AD patient, 39-fold greater than the hypothetical worst case AD patient.

For transplant recipients who develop lymphoproliferative disorder while receiving tacrolimus, the systemic exposure is 108-fold greater than the typical AD patient and 56-fold greater than the worst case.

And for the mice in the dermal oncogenicity study where lymphoma was observed, the systemic exposure to tacrolimus is 89-fold greater than the typical AD patient and 46-fold greater than the hypothetical worst case AD patient.

To summarize, the clinical pharmacology of tacrolimus ointment, we have found systemic exposure to tacrolimus in atopic dermatitis patients, even in the hypothetical worst case, is minimal, far less than that observed in nonclinical studies or in transplant patients.

For patients with detectable blood levels, there is no evidence of accumulation over time, and the levels are transient.

In our studies, pediatric patients have a lower frequency of detectable blood levels than adults and lower mean levels compared to adults, and there is a large safety margin between blood levels in the typical or even hypothetical worst case AD patient and the levels seen in transplant patients or the mouse studies.

Dr. Lawrence will now provide data supporting tacrolimus ointment as an effective and safe agent in the treatment of atopic dermatitis in both adults and children.

Dr. Lawrence.

DR. LAWRENCE: Thank you, Bill.

Dr. Stern, Dr. Wilkin, thank you very much for allowing us to present to you today.

As mentioned earlier by Dr. Johnson, my presentation will focus on the five Phase III studies which formed the core of our submission and are the primary support for the safety and efficacy of

tacrolimus ointment.

There were three randomized, double blind, vehicle controlled, 12-week studies, the 37 in pediatric patients and the 35 and 36 in adults, and two open label safety studies which involved the application of tacrolimus ointment twice daily for periods up to one year, the 25 conducted in the United States in children and the FG-12 conducted in Europe in adults.

The five core studies involved 1,554 patients with moderate to severe atopic dermatitis, 1,226 of whom applied tacrolimus ointment and 328 who used vehicle. Of these, 491 patients applying tacrolimus ointment were less than 16 years of age. Two hundred and fifty-eight of these were children less than six years of age.

In today's presentation, I will present efficacy data from the three 12-week, randomized, double blind studies and safety data from all five studies.

In the three 12-week studies, patients were randomized to apply either 0.03 or 0.1 percent

tacrolimus ointment or a vehicle as a thin layer twice daily to areas of active disease.

In patients with clearing of atopic dermatitis, treatment was to have continued for one week after clearing.

Patients were evaluated at baseline, during treatment at the end of week one, two, three, six, nine, and 12, or at the end of treatment if it occurred earlier, as well as two weeks post treatment.

As shown in this side, eligibility criteria, washout requirements, and concomitant therapy restrictions were specified in the protocol.

I'd now like to look at the results. In the three double blind, 12-week studies, a total of 983 patients, over 300 per group, were dispensed study medication and treated. More patients in the vehicle group compared with tacrolimus treated patients prematurely discontinued primarily due to lack of efficacy or they discontinued due to an adverse event.

Administrative reasons leading to discontinuation were similar across the treatment groups and included loss to follow-up, treatment

noncompliance, and patient's refusal to continue in the study.

In each study and for the overall combined data, treatment groups were comparable with respect to gender, race, age, percent BSA affected and severity of disease at the start of the study.

Of particular note is a excellent representation of African Americans and young children under the age of seven.

Please note the substantial representation of difficult to manage patients. Forty-one percent had more than 50 percent of the total body surface area affected at baseline. Fifty-eight percent had severe atopic dermatitis. "Severe" is defined by criteria published by Drs. Rajka and Langeland.

Eighty-six percent had lesions involving the head or neck, including the face.

The protocols for these studies did not restrict application area. Patients were able to treat all affected areas whether they were on the face, around the eyes, or in the intertriginous regions.

I'd like to move to the efficacy results for these pivotal trials. I'd like to begin with the results for the primary efficacy variable for each of the three vehicle controlled trials. Then using combined data from all three double blind studies, I will present the primary efficacy variable, followed by a comparison of the efficacy of the two ointment concentrations.

In the 12-week double blind studies, the primary efficacy endpoint was incidence of success obtained from the physician's global evaluation of clinical response defined as a rating of cleared or excellent improvement at the end of treatment.

This slide summarizes the analyses performed for success. An overall significant test of equal proportions among the three treatment groups allowed us to perform pair wise comparisons, primarily each concentration versions vehicle and secondary pair wise comparison was also performed versus 0.1 percent and 0.03 percent concentrations.

These analyses were performed for each individual study, for data from the three studies

combined, and for various subsets of adult patients. The population analyzed was intent to treat. All randomized patients who were dispensed drug applied it at least once.

The last observation carried forward convention was utilized.

This slide summarizes the success results for the three identically designed 12-week randomized, double blind studies. The success for each concentration was significantly higher than that in vehicle in each study, the pediatric 37, the adult 35, and the adult 36.

As you can see from this slide, tacrolimus ointment patients had a four to fivefold higher success rate than did vehicle treated patients. Success results were consistent across all studies and were very robust.

Given the consistency of these result and the identical design, we combined the data from all three of these studies. Looking at the combined success rate greater than 90 percent improvement, we see that both concentrations of tacrolimus ointment

have a significantly higher success than vehicle.

Our success criterion of at least 90 percent improvement in the physician's global evaluation is very strict. As a clinician I feel that moderate improvement represents a meaningful benefit to the patient.

The next slide shows the percentage of patients receiving 50 percent improvement or greater for the three 12-week, double blind studies combined. Similar to the result using the strict success criterion, significantly more patients in either tacrolimus ointment group showed at least 50 percent improvement when compared with vehicle, sixty-six percent in the 0.3 percent, and 75 percent in the 0.1 percent compared to 22 percent in vehicle.

Thus, about three times as many patients in either tacrolimus ointment group compared with the vehicle group showed at least moderate improvement.

Not only did tacrolimus ointment result in significantly greater improvement than vehicle, but improvement was apparent early in treatment, usually by the end of the first week.

Both concentrations of tacrolimus ointment were statistically significantly more effective than vehicle, which was confirmed by our secondary endpoints, the eczema area and severity index, or EASI score, a score developed by John Hanifin; the percent body surface area affected; physician's assessment of individual signs of atopic dermatitis; and the patient's assessment of pruritus.

In the next few slides, I'd like to compare the 0.1 percent and 0.03 percent tacrolimus ointment concentrations with respect to efficacy, highlighting comparisons only between the two concentrations and not discussing vehicle.

First, I'd like to look at the primary endpoint of success, greater than 90 percent improvement. In each individual study, the 0.1 percent concentration consistently produced a numerically higher success than the 0.03 percent.

Success for the 0.1 percent concentration was statistically significantly higher than that for the 0.03 percent concentration when data from the identically designed two adult studies were combined.

Ten percent more adult patients achieved success with this higher concentration.

The greater therapeutic benefit of the 0.1 percent concentration compared with the 0.03 percent concentration was particularly evident in adult patients with severe atopic dermatitis at baseline, as you can see in this slide.

Another primary determinant of disease severity is the percentage of body surface area affected. As shown here, as the percent body surface area affected increases, the differences in success between the two concentrations become larger, reaching statistical significance for those adult patients with greater than 75 percent BSA at baseline.

Success in the 0.1 percent tacrolimus ointment concentration was statistically higher than that of vehicle for adult females. The added benefit of the 0.1 percent tacrolimus ointment concentration was also observed in African American adults. The greater therapeutic benefit of the 0.1 percent tacrolimus ointment for adult patients was also seen in secondary efficacy parameters.

So in summary, both concentrations of tacrolimus ointment are more effective than vehicle for all patients in all efficacy parameters measured. The response is rapid, usually within one week, and in adult patients, the 0.1 percent tacrolimus ointment concentration is more effective than the 0.03 percent concentration, especially in adults with severe disease and/or extensive affected body surface area.

Data from the two open label studies support the maintenance of efficacy for the periods of up to one year.

I'd now like to focus on safety beginning with the three 12-week, double blind studies comparing adverse event profiles for each tacrolimus ointment concentration with vehicle, as well as between the two tacrolimus ointment concentrations, followed by adverse events in the two open labeled safety studies and hazard rates for the adverse events.

Safety was assessed in the five core studies based on the adverse event reporting, as well as clinical laboratory data. All adverse events were coded using a standardized COSTART dictionary and are

presented regardless of their relationship to study drug.

A total of 1,554 patients were included in the safety analyses, 983 in the 12-week, double blind studies, and 571 in our open label studies.

In the three 12-week double blind studies, nearly three times as many patients in the vehicle group compared with either tacrolimus ointment group prematurely discontinued treatment primarily due to a lack of efficacy, resulting in fewer treatment days for the vehicle group when compared with the tacrolimus ointment treatment groups.

To correct for that difference in treatment days between each of the ointment treatment groups and the vehicle group, and to present a more relevant comparison of these adverse events, Kaplan-Meier analyses that adjusted for treatment days were performed. The adjusted incident rate represents the expected incidence of a given adverse event over 12 weeks.

This slide summarizes the adjusted 12-week incident rates for adverse events observed in the

three studies combined regardless of potential relationship to study drug. A higher incidence of adverse events in the tacrolimus ointment groups compared with vehicle was generally restricted to local irritation events.

Note that vehicle and the tacrolimus ointment groups had similar incidence rates for overall adverse events, non-application site adverse events, and infections, this being a predefined cluster of infectious events.

Of particular note, fewer tacrolimus ointment treated patients discontinued due to an adverse event when compared to vehicle treated patients.

I'd next like to take a brief moment to describe the graphic presentation that I will now use. This slide illustrates the difference between two treatments and a 95 percent confidence interval surrounding the treatment difference. The circle is the observed difference and the lines represent the boundaries of this confidence interval.

If the active group and vehicle are

significantly different, the 95 percent confidence interval for the treatment group, that is, active minus vehicle, does not cross zero.

On the other hand, if there is no apparent difference between active and vehicle, the confidence interval will cross the zero line.

Here we see the 12-week adjusted incidence rates for common adverse events. The incidence in the 0.03 percent tacrolimus ointment group minus vehicle is shown in yellow. The treatment difference between the .1 percent concentration and vehicle is shown in white. Events are in decreasing order of incidence.

In most cases, the incidents of most adverse events were comparable between vehicle and either concentration of tacrolimus ointment. The exceptions are the local irritation events, skin burning and pruritus, in both concentrations and flu-like symptoms and headache in the 0.1 percent concentration group, and as noted in your briefing document, the lower incidence events of acne, dyspepsia and cyst in the 0.1 percent group and myalgia in both groups.

These local irritation events were of short duration and occurred early in treatment, generally during the first few days of treatment before the patient's skin condition had improved, and they rarely resulted in discontinuation of therapy.

Here we see the decrease in prevalence of skin burning over time. The median duration of this sensation ranged from 15 minutes to one hour after application.

Other local irritation events, such as pruritus and erythema, show a similar pattern.

This slide shows the adjusted incident rates for other adverse events of particular clinical interest: infections, based on a predefined infection cluster; flu-like symptoms; headache; fever; increased cough; and pharyngitis.

Differences between vehicle and tacrolimus ointment groups are small and do not reach statistical significance except for flu-like symptoms and headache in the 0.1 percent group.

This slide shows cutaneous events of particular interest: skin infections, folliculitis,

herpes simplex, skin tingling, alcohol intolerance, that is, patients who experience skin or facial flushing or redness or a heat sensation after alcohol ingestion, or hyperesthesia localized to the application site.

The next two slides look specifically at adverse events in children. Only skin burning and pruritus in the 0.03 percent concentration shown in yellow had a higher incidence when compared to vehicle. In the 0.1 percent tacrolimus ointment group show in white, no event had a greater adjusted 12-week incident rate when compared to vehicle.

If we continue on the next slide, you will note that the adjusted incident rate of sinusitis is actually higher in the vehicle group when compared to the 0.1 percent tacrolimus ointment group, hence the negative treatment difference shown on the slide.

This slide shows the adjusted incidence of events of particular clinical interest in our children: infection based on the infection cluster, flu-like symptoms, skin infection, sinusitis, herpes simplex, and chicken pox.

The difference in incidence among treatment groups for these events is small. The children with chicken pox did have a normal clinical course lasting from four to seven days, and all recovered fully without any clinical sequelae.

A total of 215 young children were evaluated, 143 applying tacrolimus ointment and 72 applying vehicle. These patients have an adverse event profile similar to that of the overall patient population.

No adverse event had a statistically higher adjusted incidence in the 0.1 percent tacrolimus ointment group when compared to vehicle. Only chicken pox and pruritus had a statistically higher adjusted incidence in the 0.03 percent tacrolimus ointment group when compared to vehicle.

I'd now like to turn to a comparison of the incidence of adverse events between the two tacrolimus ointment concentrations in both adults and children combined. This slide shows the adjusted incidence of the 0.1 percent group minus that in the 0.03 percent group for common adverse events. These

events are listed in decreasing order of incidence.

For these common events and for events of lower incidence not shown here, no event had a statistically higher incidence in the 0.1 percent group when compared with the 0.03 percent group.

In summary, the results of the three 12-week, vehicle controlled, double blind studies demonstrate the safety of tacrolimus ointment. There were no apparently differences between tacrolimus ointment groups and vehicle with respect to the overall incidence of all adverse events, non-application site events, or infections as defined in a predefined cluster.

Adverse events that do occur at a higher incidence than in the vehicle group are generally local irritation events of short duration occurring early in treatment. No adverse event had a statistically significantly higher incidence rate in the 0.1 percent tacrolimus ointment group compared with that in the 0.03 percent group.

I'd like to turn now to the safety of tacrolimus ointment for longer term use. These open

label studies involve the twice daily application of .1 percent tacrolimus ointment for up to one year. Patients applied ointment on average for 87 percent of their time on study, with half of the patients applying ointment for 97 percent of their days on the study.

In these studies, the majority of patients had about one-third of their body surface area affected. About half of the patients had severe disease at baseline, and the majority of these patients had head and/or neck, including facial involvement.

Of the patients included in the safety analyses for the open label studies, 465 were in the study for at least six months, and 248 for at least 12 months.

As we review safety data for these two open label studies, please bear in mind that we are looking at adverse events over a one-year period in patients with a chronic inflammatory disease.

This slide summarizes the overall adverse event incidence in the two open label studies

regardless of possible relationship to study drug. The more common application site adverse events in both open label studies were the sensation of skin burning and pruritus. The incidence of skin infection probably reflects the natural course of patients with moderate to severe atopic dermatitis.

The more common non-application site adverse events, regardless of relationship to study drug, were flu-like symptoms, headache, fever, and asthma in the children, and flu-like symptoms, allergic reactions, infection and headache in the adult study.

The adverse event profile observed in these open label studies was consistent with that expected from patients with atopic diathesis who are being observed for periods of up to one year.

The incidence of non-application site adverse events did not increase with increasing length of exposure, that is, cumulative treatment days or cumulative ointment use.

The results of both long-term, open label studies support the safety of 0.1 percent tacrolimus

ointment when used for periods up to one year in children and adults.

I'd now like to discuss the safety analyses performed using data from all five core studies which were presented in greater detail in your briefing document. In order to explore the potential relationship between drug exposure over time and the incidence of adverse events, time to onset analyses were performed using data from all five core studies, from patients applying the 0.1 percent tacrolimus ointment, a total of 898 patients.

Remember that only .1 percent was utilized in the long-term studies.

The events analyzed were those of particular clinical interest in this patient population and do not include local irritation events which have been demonstrated to occur early in treatment. Patients treated with .1 percent tacrolimus ointment in all five studies contributed to the analyses from day one through day 89, but only open label study patients were included from day 90 onward.

This slide shows the time to event analyses results for the two most common non-application site adverse events: flu-like symptoms and headache, as well as some additional events of particular clinical interest, folliculitis, herpes simplex, and lymphadenopathy.

The hazard rate analyses demonstrate that there was no increased risk to patients over time with regard to these adverse events or other events which we do not show here. The issue has been raised about whether the small numerical increase in lymphadenopathy observed over time, which is not statistically significant, but may be of clinical significance, especially in children.

There were 11 cases in children in the five core studies, with an additional two cases in the global development program. All of these cases, nine of which were in young children, resolved without interruption of treatment due to this event.

This slide shows the hazard rate for lymphadenopathy in the pediatric open label study in which children applied .1 percent tacrolimus ointment

for periods of up to one year. Note that the rate fluctuates over time.

I think it's important to point out that most of the events COSTART coded as lymphadenopathy or lymphadenitis secondary to an inflammatory process, such as tonsillitis or a concurrent skin infection. The investigator's terms which were eventually coded as lymphadenopathy includes small cervical enlargement, palpable or shotty cervical lymph nodes, infected lymph glands, et cetera. All of these were short-lived enlargements and are not uncommon in patients at atopic dermatitis, especially children. They appear to represent little clinical concern since none of these events were associated with an unexplained profound weight loss, fever, night sweats, or progressive generalized node enlargement which might signal a significant pathology.

Of the 33 cases of lymphadenopathy observed for the 4,205 patients treated with tacrolimus ointment in our global development program, an incidence, by the way, of about .8 percent. Only one event named axillary lump could not be explained.

Therapy was not continued, however, for this patient, and they did resolve spontaneously.

There have been no cases of lymphoproliferative disease in children in the tacrolimus ointment development program to date. Two cases of lymphoma have been observed in the global tacrolimus development program in adults.

A B cell lymphoma in a 68 year old presented in the parotid and was diagnosed as low grade follicular lymphoma of the type not generally associated with immunosuppression. It is also important to note that this mass was present at the time of entry into the study.

And mycosis fungoides. This is a patient who had eczematous dermatitis for seven years, diagnosed initially as atopic dermatitis at the age of 51 with his initial presentation. This suggests that this may well have been his initial presentation for CTCL.

Both cases of lymphoma occurred in adult patients. Both cases were considered by the managing investigator to be unrelated to the treatment with

tacrolimus, and in both cases the patients responded fully to treatment.

In all five core studies, standardized hematology and chemistry parameters were evaluated in all adult patients and 56 percent of children. No trends in laboratory profiles suggestive of a safety concern were observed in either the 12 week or the open label studies.

As might be anticipated in patients with atopic dermatitis, eosinophil counts, IgE, and LDH were elevated in many patients at baseline and remained so during the studies.

Based on the results of the five core studies, the risks associated with the use of tacrolimus ointment are minimal and do not increase with use up to one year.

Adverse events are generally local irritation events of short duration, usually occurring early in treatment. In control trials, there were no statistically significant differences between the vehicle and tacrolimus ointment groups with respect to overall incidence of non-application site adverse

events or events in the predefined infection cluster.

No trends in clinical laboratory profile were observed.

The safety profile observed in the five core studies is consistent with that observed in support of global studies as were provided in the NDA.

The FDA has proposed several questions to you today, and I would like to present our responses to these questions, as well, since Dr. Wilkin was kind enough to present them to us yesterday.

The first question, is Protopic, 0.03 percent, effective in the treatment of atopic dermatitis? We believe yes. In the three, 12-week, double blind, vehicle controlled trials involving over 300 patients in each study, 0.03 percent tacrolimus ointment was significantly superior to vehicle.

Is Protopic, 0.1 percent, more effective than Protopic, 0.03 percent, in adults? We again believe yes. In the two double blind, vehicle controlled studies involving 632 adults, 0.1 percent tacrolimus ointment was significantly more effective, particularly evident in patients with severe disease

and extensive body surface area involvement.

Is Protopic, 0.1 percent, more effective than Protopic, 0.03 percent, in children? No. In our pediatric trials involving 351 children, there was no significant difference in efficacy between the two concentrations.

Is Protopic safe for unrestricted chronic therapy as a first line treatment in adults for both concentrations? Yes. The safety of the 0.1 percent concentration of tacrolimus ointment in adults has been established for up to one year, and thus established the safety concurrently for the lower concentration of 0.03 percent.

Is Protopic safe for unrestricted chronic therapy as first line treatment in children for both concentrations? Again, we believe yes. The safety of the 0.1 percent concentration of tacrolimus ointment in children has been established for up to one year. As for adults, we have also by inference established the safety of the lower 0.03 percent concentration.

The next question responds to unrestricted chronic therapy versus time limited acute therapy. We

believe that unrestricted chronic intermittent therapy is the most appropriate use of this drug. We would recommend, as conducted in our clinical trials, that patients should treat each episode to clearing plus seven days and then discontinue treatment.

First line therapy versus second line treatment. We believe that first line therapy is appropriate. Tacrolimus ointment represents the first new topical treatment for atopic dermatitis in several decades and offers significant benefits over conventional treatments which have well known adverse events. Physician and patient should have the option of utilizing this important new agent as first line therapy to treat this debilitating and very life altering disease.

With respect to the concentrations, 0.03, 0.1, both or neither, the 0.03 percent tacrolimus ointment achieved a maximal efficacy in children. The 0.1 percent tacrolimus ointment showed additional therapeutic benefit only in adults and particularly those with severe disease and extensive body surface area involvement.

The safety of 0.1 percent tacrolimus ointment has been established for up to one year. Therefore, the data support the approval of the 0.03 percent concentration in children and both concentrations in adults.

Are there additional studies needed for the labeling of Protopic? And what are they? We believe that the NDA data we have summarized here today have clearly demonstrated the safety and efficacy of tacrolimus ointment for the treatment of the signs and symptoms of atopic dermatitis in adults and children.

We also believe that the depth and breadth of this information is sufficient to provide clear labeling for this product.

However, with any approved drug, Phase IV investigations after approval will provide further useful information.

We would also like to make a few further recommendations for the use of tacrolimus ointment. Patients should minimize or avoid unprotected exposure to natural or artificial sunlight during therapy.

The use of tacrolimus ointment has not been shown to increase the risk of developing lymphoma. However, to be prudent, patients who have unexplained fever or unexplained lymphadenopathy, or who have suspected or proven infection mononucleosis should delay the start of tacrolimus ointment therapy or interrupt therapy until these symptoms have resolved.

We believe tacrolimus ointment represents a novel, safe, and effective nonsteroidal topical therapy for the management of atopic dermatitis.

Thank you very much for your attention.

We'd now like to answer questions, and Dr. Fitzsimmons will join me at the podium.

ACTING CHAIRMAN STERN: Thank you very much for a very clear, succinct presentation, and especially all aspects of it, including your final summary.

DR. LAWRENCE: Thank you very much.

ACTING CHAIRMAN STERN: Questions from the committee?

DR. MINDEL: Was there any attempt to

correlate blood level with effectiveness therapy?

DR. LAWRENCE: Yes, and I will ask Dr. Fitzsimmons, please.

DR. FITZSIMMONS: Yes. We performed an analysis to evaluate the success rate, and if I could have slide number 269, please.

In this analysis, we looked at patients who had quantifiable levels versus those who did not and compared their success rate on the primary endpoint, and as you can see, for the overall population there is no difference: 33 percent success rate in those with a quantifiable level versus 36 percent in those without. And this is similar also whether you look at subsets of moderate or severe.

DR. MINDEL: I'm not sure that's exactly what I was asking. I was asking whether the level in terms of as the level increased was there a difference rather than sort of grouping, grouping together. Your numbers seem to small to me to be able to do that.

DR. FITZSIMMONS: Yes. What we tended to see is that patients when they start therapy have their flare of atopic dermatitis. At that time is the

most frequent time where you see quantifiable levels. As that flare subsides and the therapy is effective, the skin barrier becomes more effective and there is lower quantifiable levels. You tend to see early levels in those few patients that have them, and then they drop off quickly as the topic dermatitis improves.

DR. LAWRENCE: And I think, Dr. Mindel, the point you made is very important. One of the difficulties with that particular analyses, there were so few patients that has measurable levels that it's very difficult to really draw any strong inference with regard to the level and efficacy over time. At least most of them were only a single event.

DR. LIM: A question about the slide 15 on the light source, the photocarcinogenesis study. What type light source was used for the mouse model study?

DR. FITZSIMMONS: This was a UVR light source, and maybe I could ask Dr. Forbes to clarify exactly how this was done. He had performed this, developed this model.

DR. FORBES: Thank you.

The light source is a xenon arc, a long arc solar simulator that includes both the ultraviolet and the visible portion of the spectrum. I can give you any more detail that you would like to have, but I don't want to bore you with it.

DR. LIM: So it covers both UVB as well as visible light?

DR. FORBES: Yes. The UVB and UVA in approximately the proportion that one would see at about 35 degrees north latitude in the summer.

DR. LIM: And could I have a follow-up question?

ACTING CHAIRMAN STERN: Of course.

DR. LIM: On the photosensitization, you mentioned there was no evidence of photosensitivity. You mentioned specifically phototoxicity, but then you also mentioned about photosensitization. Is that photocontact allergy, the protocol that you used?

DR. LAWRENCE: Yes. I'm sorry. That wasn't clear. Yes, that's photocontact allergy in the protocol.

DR. LIM: Thank you.

ACTING CHAIRMAN STERN: Thank you.

Dr. Bigby.

DR. BIGBY: I actually have a couple of questions. The first thing, I'd like to compliment you on in your toxicity data showing rate differences with 95 percent confidence intervals, and I was curious to know why you didn't present the efficacy data that way as well, comparing drug and placebo and the two concentrations.

DR. LAWRENCE: I think it was just a graphical presentation choice. I apologize for that. I do.

DR. BIGBY: Yeah, because I think it would be helpful because it would show not only the magnitude of the differences, but the precision, and I think it would be quite revealing to have that available.

DR. LAWRENCE: Actually, I can. If I could have slide 872, these are the differences based on success rate.

I apologize. I'm guilty for that. I like the graphics better.

But here you see the treatment differences and success rate. I apologize. I don't have a pointer, but at the top is the two adult trials, and at the bottom are the pediatric trials, and you can see the first line is the .03 percent concentration.

Oh, thank you very much.

This is the .03 percent concentration here, and then the .1 percent concentration here in these studies.

DR. BIGBY: Okay. So there's similar data for the difference between .03 and .1?

DR. LAWRENCE: I'm not sure if we have those data. Let me just see. If I we, I'll be happy to show you.

We do not have those. I apologize.

DR. BIGBY: Okay. Another series of question. What incidence of tacrolimus-associated lymphoma would you find unacceptable?

DR. LAWRENCE: I think any tacrolimus-associated lymphoma would be unacceptable to us. We believe that this is an important issue, especially in children, but I think the challenge for us will be to

definitely have a clear relationship between the lymphoma and the tacrolimus, especially in some patients who have been treated with other potentially bothersome products, such as oral cyclosporin or other oral immunosuppressive agents, as well as some light therapies, as well, which we do know have immunosuppressive agents, as well.

DR. BIGBY: So that means that if after the drug is approved there's a case of tacrolimus-associated lymphoma, you'd come back and say you wanted to take it off the market?

DR. LAWRENCE: Well, I think, again, that would be a difficult question to answer. I would say that certainly we do not wish to have and do not believe that there is a risk of lymphoma, based on our current data. I don't think I'm prepared to make a specific statement about what the level would be. I think we'd certainly want to work with the agency on something like that and develop guidelines.

I apologize for my misstatement earlier.

DR. BIGBY: So then the other part to that question is, you know, based on your current

estimates, what's the upper 95 percent confidence interval of your estimate of the risk of a patient developing a lymphoma while using tacrolimus?

DR. LAWRENCE: Bill, would you like to address that?

DR. FITZSIMMONS: Well, at this point the incidence is zero. There are no cases in our total database. So we have not calculated a confidence interval around that zero. There is --

DR. BIGBY: But you can, you know. You can based on the number of patients exposed and their length of exposure.

DR. FITZSIMMONS: We just have not calculated that confidence.

DR. BIGBY: Okay. Can I do a couple more?

How was African American defined in your study?

DR. LAWRENCE: This was on the case report forms. Patients were asked to be identified by the managing physician as either Caucasian, Oriental, African American, Latino or Hispanic or Other. So it was left up actually to the individual managing

physician.

DR. BIGBY: Okay, and so given that, do you have any biologic explanation for why one percent was more effective or .1 percent was more effective than .03 percent in patients who were self-defined as African American?

DR. LAWRENCE: We actually have looked at that. I am not aware of a strong biological reason. There certainly is evidence in the clinical literature that in some cases African American or other patients of color do benefit from different strengths of drugs or different concentrations of topically applied drugs.

I'm afraid I don't have a very strong reason for that observation other than to just say that we did see it, and we noted it consistently in the adults.

DR. BIGBY: Did you adjust for severity in looking at differences between racial groups?

DR. LAWRENCE: We did adjust both for severity and also other characteristics, such as erythema, et cetera.

DR. BIGBY: And this is my last comment.

DR. LAWRENCE: That's okay. Please.

DR. BIGBY: You talked about combining the results of studies. Was that just done by sort of adding the total number of patients and sort of recalculating it based on, you know, totals?

Because that's actually not a correct way to combine studies.

DR. LAWRENCE: Perhaps the best thing for that since I claim not to be a statistician is to as Mr. Yoichi Satoi, who is the statistician to come up and specifically address that question. I don't want to misstate anything.

DR. SATOI: My name is Yoichi Satoi. I'm a statistician.

Could I clarify in terms of efficacy analysis or safety analysis?

DR. BIGBY: Efficacy.

DR. SATOI: Efficacy. Actually our efficacy analysis combining studies based on stratified analysis, study as a strata. So it means study is taking into account of (unintelligible), not

just the overall crude analysis, but kind of a combined study.

DR. BIGBY: So, you know, in meta analysis when you combine studies, you either do it based on random or fixed effects models. Is this what you did?

DR. SATOI: We used stratified analysis using a Mantel-Haenszel type approach. So it means we used study as a fixed effect.

DR. BIGBY: Thank you.

ACTING CHAIRMAN STERN: Dr. Epps.

DR. EPPS: Thank you.

I just have a brief question. There were in your thorough booklets and in presentation -- thank you very much for that -- there was a discussion of herpes zoster infection, and five of the cases were reported as chicken pox in kids. Was the immunization status of all the kids -- were they all up to date when they entered the study, and had these kids been immunized?

DR. LAWRENCE: I apologize. I truly do not know that.

DR. EPPS: Okay.

DR. LAWRENCE: We did not collect that information with regard to immunization status. So I really can't answer that. I apologize. Certainly we can try and get that.

DR. EPPS: Well, I would be curious about the ones who did present, who did evolve or had chicken pox, whether or not they had been previously immunized.

Thank you.

ACTING CHAIRMAN STERN: Other questions from other committee members? Dr. Tang.

DR. TANG: Yeah, this is Ming Tang.

I have a question on the efficacy study. So you have used, as I understand, you have used the intend to treat analysis, and it is stated in slide 36 that 64 of the patients discontinued. So at the end of 12 weeks, how many patients were included in your analysis?

DR. LAWRENCE: Well, all of the patients were included. We did --

DR. TANG: So you were able to evaluate them at 12 --

DR. LAWRENCE: Yes, we used a last value carried forward. So if the patient left the study at whatever week and they were counted as a failure, that failure was carried forward. That was true of all treatment groups, so that we did have a full number of patients to evaluate from the efficacy standpoint.

ACTING CHAIRMAN STERN: Other questions from committee members?

(No response.)

ACTING CHAIRMAN STERN: Then if it's all right, I'd like to ask a few.

DR. LAWRENCE: Please.

ACTING CHAIRMAN STERN: I guess one is on the .03 versus .1 percent in adults. I noted that there was a difference in dropout rates, higher in the .03 than the .1, and you appropriately used intention to treat, but, in fact, I wonder if you used people -- and the reasons for drop seem to be quite independent of the drug where there were differences -- I noted you used intention to treat, and in fact, I wondered what would happen to success rates if you only used individuals who, in fact, completed therapy in the

final analysis.

That would tend to lower the difference in the proportion of individuals improved between the .03 and .1, and since your P was only .04, it may have made that a nonsignificant effect.

DR. LAWRENCE: I'm not sure if we have those analyses done. I will wait till my crew comes --

ACTING CHAIRMAN STERN: It's just that when you're very close on making significance, I think you have to look at other things that might have affected your analysis, although you did the appropriate one, and I think that's something to keep in mind in the arguments.

DR. LAWRENCE: Thank you. That's a very good point.

ACTING CHAIRMAN STERN: Sir, could you -- sure.

DR. FITZSIMMONS: If I could make one clarification on that. Can you display slide 858?

If you look early on, before the end of treatment, you can see that at each evaluation time

point in these studies and before many of the discontinuations occur there is a continuous difference between the yellow bar here, which is a .03, and the .1, which tends to get greater over time.

That's not an analysis of only the completers, but tends to show that even before dropouts occur, that difference starts.

ACTING CHAIRMAN STERN: I have a number of in a sense safety related questions, some of which are informational. One is I noticed in the children, the area of application was, I believe, 50 to 100 square sonometers, and that when I did my math to bring it back into the English system is essentially between a three inch square and a five inch square, not a large area of application, if I read that slide correctly. Did I?

DR. LAWRENCE: Yes, that is correct just for the 08 pharmacokinetic study.

ACTING CHAIRMAN STERN: I understand, but in terms of the data where we're getting systemic absorption, we're talking about areas no larger than this. That's about 100 square sonometers.

What I'd be interested in is do you have any data looking at the skin in terms of T cell profiles, in terms of cytokines, in terms of what's going on when, in fact, you treat an individual with atopic dermatitis when both initially and when they're cleared with this product systemically and topically?

DR. LAWRENCE: We do not have a comparison between systemic and topical tacrolimus. We did conduct a very small study that was actually presented last year at the Society of Investigative Dermatology, comparing some cytokine markers in the skin in patients with atopic dermatitis looking at triamcinolone versus tacrolimus, and in that study there was obviously diminution in several cytokines. A greater number of cytokines were actually diminished with triamcinolone versus tacrolimus.

In all of those patients they were treated for three weeks, measured at baseline, week three, and then stopped, and then measured again at two weeks post.

What we found was that the IL-13 was diminished significantly in the tacrolimus treatment

arm and similarly also in the triamcinolone arms. However, in the triamcinolone arm we also saw decreases in other markers, including Langerhans cells and macrophages, which we did not see that change in the tacrolimus arm.

We don't have, unfortunately, Dr. Stern, any comparison to systemic and topically.

ACTING CHAIRMAN STERN: I guess from a safety point of view to me the most direct way, aside from studies in humans, to approach this issue of at least skin cancer is to really look at to what extent are there changes that are measurable in the skin that are comparable between the topical agent and where the oral agent is used because I think many of us would believe that much of what might go on with respect to the promotion or permission of at least squamous cell carcinoma is like to be events in the skin rather than events that would be reflected in systemic levels.

And I guess the next question is really a little bit extending on Michael's question. In terms of lymphoma in transplant patients, I don't have a good concept of -- I think I heard you say that two

years is the mean or median time of onset. Could you educate us about age groups at risk and how long it takes to manifest itself?

DR. FITZSIMMONS: Yes. In the transplant setting, again, where they have chronic maintenance immunosuppression with multiple agents, such as tacrolimus, steroids, azathioprine or mycothenolate, the incidence of PTLD is less than five percent. It depends on the organ transplant that you look at.

The median time to onset in our tacrolimus database, which is quite extensive, is 122 days post transplant, and the risk factors, the main risk factors relate to the age of the patient, with pediatric patients being at higher risk based on their EBV serology than adult patients. But these tend to be early events, usually within the first year post transplant.

ACTING CHAIRMAN STERN: Have you looked at your data to see if there's any relationship between mean or median time to the event and dosage of the drug or, for example, comparing livers, kidneys and hearts, where there tend to be very different

maintenance levels of doses?

DR. FITZSIMMONS: There is a relationship between the blood concentration of tacrolimus and the risk of post transplant lympoproliferative disease in these patients, and that's across kidney, liver, and the solid organs.

ACTING CHAIRMAN STERN: But my question was sort of an extension on that. If you take people who have lower systemic levels, do they have a longer mean time?

What I'm sort of asking is: do we know if there's really a threshold here, and may it be a product of concentration times time that's important?

DR. FITZSIMMONS: The main factor in that onset time is actually the primary EBV infection, which oftentimes occurs because of the organ that's transplanted being EBV positive or the blood products that are given. So that the time onset is really related to the EBV, not necessarily to the duration of the systemic immunosuppression.

ACTING CHAIRMAN STERN: Thank you.

One issue, I think, for all of the safety

things is you have -- and this is both a comment and a question -- you have a one-year database. My understanding is that these individuals use this drug on an as needed basis. So, in fact, the total time of exposure in most cases is likely to be substantially less than 365 days.

My first question is: what were the quantities used? I assume in all of these trials, especially the long-term ones, you had people bring back the tubes, and you have some idea of how much was applied. Could you give us some idea of the range of amounts of product, the mean?

DR. LAWRENCE: I'll get away from my slides to come up here, but, yes, we have, indeed, collected those data in both the short-term and long-term studies.

While we're waiting for those data, it's also important, Dr. Stern, that in the long-term studies, the average number of days on study was actually about 270 days. So many patients chose to continue on the drug even though they had to have some lesions clear.

Also, frequently what we see is that patients will clear in one area and they'll have a breakthrough in the other, and they'll just continue to apply. Actually the mean number of treatment days in the long-term pediatric study was 279, if my memory serves me pretty well.

If I could have slide 298, please, this addresses your question, Dr. Stern, and I'm going to have to put glasses on. I apologize.

ACTING CHAIRMAN STERN: Yeah. I'm having trouble, too.

DR. LAWRENCE: You see here, again, the number of treatment days, and these are the pediatric and adult 12-week trials first off. So these are only 12 weeks, which should give you a little idea. I'm sorry, yeah.

The total grams used was about the same in the vehicle, the 0.03 and the 0.1 percent group, in pediatric patients, around 280 to 300 grams.

The adults, as you can imagine, had a higher number of grams used. This is primarily, I think, because they just stopped, and when we

calculate the total amount used, they certainly had a larger body surface area and used it for shorter periods.

If you look at the average daily ointment use in grams, you can see interestingly that actually the vehicle patients used more. I don't know if they were trying to add more for benefit or not, but certainly about, on average, about four grams in the children and about six grams in the adult patients for an average of about five and a half.

And you can see the BSA at baseline was comparable across the board.

If we look at slide 297 --

ACTING CHAIRMAN STERN: Could I ask a question right there?

DR. LAWRENCE: Oh, certainly. Please. If we could put slide 298 back, please.

ACTING CHAIRMAN STERN: To me it's very interesting that, if I can read it, in adults -- I'm sorry. I can't. Could you tell me what the -- I'm not sure I can read whether that's six or what the mean, the daily ointment use.

DR. LAWRENCE: The daily ointment use during treatment in adults is about -- in adult patients is 9.6 in vehicle and 6.2 and 6.4 in the treatment group.

ACTING CHAIRMAN STERN: Okay. So about six.

DR. LAWRENCE: Yeah, about six.

ACTING CHAIRMAN STERN: I'm sorry. It's difficult for me to read.

DR. LAWRENCE: No, that's okay. I'm having trouble, and I'm standing in front of it.

ACTING CHAIRMAN STERN: And I see that the percent body surface area was nearly half the body.

DR. LAWRENCE: Yes, that is correct.

ACTING CHAIRMAN STERN: And this is a twice a day application.

DR. LAWRENCE: Yes.

ACTING CHAIRMAN STERN: The usual rule of thumb is that it takes about 15 to 30 grams to cover in one application your entire body surface area, and this is suggesting that you're using about three grams each application to treat half the body surface area.

That actually comes to a question I had earlier. I found this distribution of extent of body surface area to be quite extraordinary for a clinical trial. I think it was about 70 percent of individuals had more than 20 or 25 -- more than 25 percent of body surface area involved, and about 20 percent had more than 75 percent of body surface area involved.

I'm wondering exactly how you documented and counted body surface area because these are at least in my clinical experience quite extraordinary amounts of truly affected area for atopic dermatitis.

DR. LAWRENCE: If I could actually to answer that question, let me have slide 390, please.

Again, these are the double blind studies, the 12-week studies, and these are pooled data. You can see here the distribution of baseline body surface area, 30 percent, ten to 25, et cetera.

ACTING CHAIRMAN STERN: Right.

DR. LAWRENCE: And I don't need to read them to you.

In overall about 46 percent of the patients -- 46 percent of the patients BSA was

affected at baseline. I think one issue on the slide for the exposure is the way we've calculated, it artificially, I think, lowers it.

What we know is that as the patients get better, the BSA decreases. The amount used on a daily basis diminishes. When we calculate these numbers, we take the total amount used, divide it by number of days, and that's an average daily. So I think it's probably a little bit of a misrepresentation. I apologize for that confusion.

We know that you certainly see more in the beginning and much less as the patients get better and BSA decreases.

ACTING CHAIRMAN STERN: I guess though my question was here. This is to me an extraordinary distribution of extent even if you're looking for severe individuals. I'm one of those individuals who uses some of these other modalities to treat severe atopic dermatitis, and the proportion of adults that we see, in fact, with terrible atopic disabling disease, who really at any given time have more than half their body affected in terms of BSA, is quite

small, even in a very self-selected population of people who have come to very invasive therapies.

So I just wondered how you could recruit these individuals.

DR. LAWRENCE: I think maybe the best thing there, Dr. Stern, Dr. Amy Paller is one of our investigators, and I think she has a greater familiarity with the calculations.

ACTING CHAIRMAN STERN: She's a pediatrician though.

DR. LAWRENCE: Yes, but she has --

ACTING CHAIRMAN STERN: I'm more concerned about the adults because these are really --

DR. LAWRENCE: Yeah.

ACTING CHAIRMAN STERN: In kids I've seen it, but in adults it's quite extraordinary.

DR. LAWRENCE: It was. It was based on the calculation of body surface area using a homunculus, and the investigator's determination at baseline. So, again, it was investigator driven. We did not calculate those numbers.

I don't know though if it would be

helpful. Dr. Paller could comment on the severity of the patients we enrolled. They were quite dramatic.

Amy, maybe you'd like to comment on that. It's easier to -- unfortunately the room's acoustics are not very good.

DR. PALLER: Yeah, the question is really different here because Dr. Stern's question was about adults, and my experience is pretty much exclusively with children, where I think everyone would agree we not uncommonly will see children who have extensive body surface area involvement.

ACTING CHAIRMAN STERN: Could I ask other panel members, you know, who take care of atopic dermatitis if you see them very often with truly more than half their body involved, not a patch here and a patch there, but actual coverage?

DR. ABEL: Well, often when I see patients with very extensive atopic dermatitis, those are patients who often have superficial impetiginization. they're excoriating, and their atopic dermatitis has become more widespread, and those are also patients who respond to systemic antibiotics.

And that brought up a question to my mind, also relates to safety. How were these patients assessed for infection, signs of superficial impetiginization or infection, and how that would relate to decreasing the risk of folliculitis, bacterial superinfection, and all of the other.

I know this is separate questions mixed up together, but I suppose also in response to Dr. Stern, I think, and one reason for it to be widespread would be secondary infection, but also these patients are very xerotic. They have very dry, scaly skin, and perhaps that's taken into account with assessment of body surface area because sometimes, I mean, these lesions, unlike psoriasis, are poorly marginated, and there's diffuse involvement with xerosis.

So I think it might be difficult under a number of circumstances to really define body surface area, the way one would do it with psoriasis, where there are discrete blacks (phonetic).

But I am interested in how patients were assessed for infection. Were they treated with antibiotics first? Do you exclude patients who have

active excoriations and crusting?

DR. LAWRENCE: We did not exclude patients with excoriations or crusting. At the time of enrollment in the study, we did exclude patients who are actively infected, assessed by the managing physician.

During the course of the study if they did get infected, they were permitted to use systemic antibiotics as part of the treatment, and as you saw in the data that I presented, the number of skin infections actually was quite similar across the three treatment groups, vehicle and the two tacrolimus treatment groups. It was running about 11 percent total, which is, I would think, would probably be low or in the range that you would anticipate with these patients, especially chronically.

But we -- and certainly in the long-term studies at least, the incidence rate of infection was about 11 percent. We actually had a greater number of skin infections in the patients in the 12 week study in the vehicle group compared to the tacrolimus ointment group.

As far as inter -- and I'm sorry. I have trouble with that word -- the impend --

DR. ABEL: Secondary -- superficial secondary infection.

DR. LAWRENCE: Thank you. That's much easier, needless to say.

We did require that patients not be actively infected at the time of enrollment. That was just the decision we made because at that time we didn't know what other issues may arise with the treatment of the drug, and we were being, I think, relatively conservative.

Did that answer your question or is there anything else I can answer, Dr. Abel? I'll be happy to try.

DR. ABEL: Well, in many of these, oftentimes patients with severe, widespread atopic dermatitis need systemic antibiotics. So I was wondering how many have required that prior to entry of the study.

DR. LAWRENCE: We only have data for the 30 days prior to the study. Most of these patients

had required, I will tell you from history, systemic and topical antibiotics, systemic and frequently in especially the adults systemic corticosteroids. So these were very severe patients at baseline, and in fact, if I could have slide number 820, that may answer some of your questions.

ACTING CHAIRMAN STERN: There was an exclusion criterion though about recent use of systemic antibiotics.

DR. LAWRENCE: Right, exactly.

ACTING CHAIRMAN STERN: So these are not individuals who at the time of enrollment --

DR. LAWRENCE: That is correct. Yes, that is correct.

So what you can see here though is that within the 30 days prior, a fair number of patients, about eight percent, had taken systemic antibacterials during that period. Again, you can see systemic corticosteroids.

These were very severe patients, and were certainly very difficult to manage obviously in the baseline state.

Does that answer your question, Dr. Abel?

DR. ABEL: Thank you.

DR. LIM: I have a question on your slide number 90, where you did say that this is the first line therapy in adults and children of two years of age.

Since you did not do a sort head-to-head comparison between tacrolimus and the more traditional treatment for atopic dermatitis, how did you come to the conclusion that this should be used as a first line therapy?

DR. LAWRENCE: I think, Dr. Lim, that really is maybe partially a semantic issue. We believe that this should be an option for patients who require treatment for their atopic dermatitis and should be one of the options available to physicians at the time that they're making a determination.

The majority of our patients actually have been treated for many years. Previously many of them had actually failed previous conventional therapy.

I think the issue about the first onset of disease, which would obviously only impact the

youngest of children, I think still we believe that the safety and efficacy have been adequately demonstrated enough that even the physician, we believe, is in the best position to really make a risk-benefit determination on which particular drug or product would be appropriate for that particular patient.

That's really how we're persisting in the concept of first line therapy.

ACTING CHAIRMAN STERN: I'd like to ask two last questions. One is since this is an often lifelong disease, are safety data for one year sufficient to feel confident about the long-term risks of low dose exposure and localized exposure to this immunosuppressive agent.

And the second, related to that, is -- perhaps Dr. Forges might address this -- is what might be the models that might, in fact, address the issue not of simultaneous UV and change in the risk of skin cancer, but the risk of skin cancer with long-term use in people who have had substantial prior UV or risk characteristics, putting them at higher risk for non-